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OP0094

SECULAR TRENDS IN THE INCIDENT RISK OF CEREBROVASCULAR ACCIDENT IN RHEUMATOID ARTHRITIS RELATIVE TO THE GENERAL POPULATION

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Background: Recent studies have demonstrated a declining trend in RA mortality relative to the general population (1). This improvement in mortality could be due to improvement in incident risk of cardiovascular events that are the leading cause of excess deaths in RA (2).

Objectives: Our objective was to assess secular trends in ten-year incident risk of cerebrovascular accident (CVA) in incident cohorts of RA versus general population controls, using administrative health data.

Methods: We conducted a retrospective study of a population-based cohort of incident RA cases who first met previously published RA criteria between 01/01/1997 and 31/12/2004 in British Columbia followed until 31/12/2014, with general population controls matched 2:1 on gender, age, and index year. Individuals were excluded if they had a diagnosis of CVA prior to index date. Incident CVA was defined as first CVA during follow-up using ICD codes 9 code 433, 434/ICD-10 code I64, I63) in Hospital Discharge data or death certificate in Vital Statistics data. RA and general population cohorts were stratified according to year of RA incidence, defined according to first RA visit, using a 7-year wash-out period. Incident rates (IRs) of CVA for RA and general population cohorts, as well as incident rate ratios (IRRs), with 95% confidence intervals (CI) were calculated per calendar years of incidence. Multivariable Cox Proportional Hazard models with left truncation were used to estimate risk of CVA in RA relative to general population while controlling for potential confounders, with contribution of person time of follow-up starting from index date (second RA visit) to avoid immortal time bias and censoring at ten years from incident year, or last health care utilization. To examine whether secular trends differed in RA relative to general population, an interaction term was tested between the RA indicator and year of RA incidence. To account for non-linear effect of cohort year, we compared cox regression models with linear, quadratic, and flexible spline forms of the cohort-year effects and the model with the best AIC was used to interpret the data.

Results: 23,545 RA individuals (65.7% female; mean [SD] age 58.11[16.82] years) and 47,090 controls experienced 658 and 1,220 incident CVA respectively. A linear spline Cox model with a knot at year 1999 was selected to fit the CVA events. The change in CVA risk over time differed significantly in RA vs. general population after 1999 [$p=0.0488$], but not before 1999 [$p=0.06$]. A significant decline in risk of CVA was observed over the calendar years of incidence after 1999 in RA [0.91 (0.86, 0.96); $p=.0003$] but not in the general population [0.97 (0.93, 1.01); $p=0.1019$].

Conclusion: Our findings suggest that the risk of CVA has significantly declined over time in people with RA onset from 1999 onwards, but not in the general population.

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OP0095

INFLUENCE OF PERIODONTITIS ON DISEASE ACTIVITY, PHYSICAL FUNCTION, AND SAFETY IN PATIENTS WITH RHEUMATOID ARTHRITIS: A OBSERVATIONAL STUDY USING THE IORRA COHORT

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Background: Periodontitis (PD) is considered to be one of the triggers for rheumatoid arthritis (RA) ¹. Several reports demonstrated the associations between the disease activity of RA and presence of PD, however, most of them are based on small population, and results are inconsistent ^{2, 3}. Furthermore, impact of PD on physical function and safety is not known. Thus, a study using a large cohort database is warranted to clarify the relationship between patients' outcomes and PD among patients with RA.

Objectives: To demonstrate the influence of PD on the outcome of RA, an established cohort IORRA database was used to compare the disease activity, physical function and prevalence of infection between patients with PD and those without.

Methods: IORRA database is an established cohort database with RA in our institute since 2000. Trough biannual data collection including patient's questionnaire, physician's evaluations and laboratory data in more than 5,000 RA patients, a database with a total 91,884 patient-year observation period was established by 2018. In this IORRA database, RA patients who answered to all the questionnaires about PD in October 2016 were extracted. Among those, we defined patients with PD (PD group) as having diagnosis of PD during the last 6 months, and those without PD (non-PD group) as having no present and previous PD. Using the data set from April 2016 to October 2016, we compared Disease Activity Score 28 (DAS28), Japanese Health Assessment Questionnaire (J-HAQ) score, and the prevalence of patients self-reported infections required hospitalizations or hospital visits between the two groups. For background data comparisons, we used chi-squared test for categorical data and Mann-Whitney U-test for continuous data. To investigate associations between PD and remission or PD and infection, we calculated adjusted odds ratio (OR) of PD using a logistic regression model.

Results: At baseline, patients in the PD group ($n=925$) were significantly older, had higher DAS28 and J-HAQ than those in the non-PD group ($n=2,583$). DAS28 and J-HAQ at 6 month in the PD group were significantly higher than those of the non-PD group (DAS28, 2.60 in PD group, 2.42 in non-PD group, $p<0.001$; J-HAQ score, 0.25 in PD group, 0.13 in non-PD group, $p<0.001$). Median of delta DAS28 and delta J-HAQ in the both groups were similar and adjusted ORs of PD for DAS28 remission (0.85 [0.69-1.04]) and for J-HAQ remission (0.99 [0.67-1.45]) at 6 month were not statistically significant. There were significant differences in the percentage of patients who developed infections between the two groups (5.8% in PD group, 3.4% in non-PD group, $p=0.002$). Adjusted OR of PD for infections was 1.72 [1.10-2.69], which was significantly elevated.

Conclusion: RA patients with PD had similar treatment response with those in the non-PD group, however, had higher disease activity, poorer physical function, and higher risk of infections compared to those without. These results may indicate that oral management is important for the better outcomes of patients with RA in the daily practice.

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Tackling chronic pain; fibromyalgia and back pain__

OP0096

DYSREGULATED BONE MARROW STROMAL CELLS IN MODIC TYPE 1 CHANGES

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Background: Modic type 1 changes (MC1) are fibrotic-inflammatory vertebral bone marrow lesions adjacent to degenerating discs. Patient with MC1 often develop low back pain [1]. In MC1, extra-cellular collagen is deposited, myelopoiesis is dysregulated, and bone is rapidly remodeled. These are signs of a chronic inflammation. The cellular mechanisms are unknown, yet bone marrow stromal cells (BMSC) are key regulators of myelopoiesis, can differentiate into collagen-producing cells, and modulate inflammation [2].

Objectives: To link BMSC phenotype and function to molecular changes in MC1.

Methods: From patients undergoing lumbar spondylodesis, bone marrow aspirates (n=5 MC1+5 controls, adjacent level healthy bone marrow (Ctrl)) or biopsies (n=2 MC1+2 Ctrl) were taken through pedicle screw trajectory before screw insertion.

Biopsies were fixed, dehydrated, and imaged with multiphoton fluorescence microscopy (MPE). Tissue auto-fluorescence and second-harmonics-generation (SHG) of collagen were recorded of full-length biopsies with up to 200 µm penetration depth and qualitatively evaluated. Fluorescence-life-time-imaging-microscopy (FLIM) of the auto-fluorescence signal was performed in key areas of biopsies and single-photon-counting histograms were fitted with a triple-exponential decay function.

BMSC were isolated from aspirates by plastic adherence and characterized (passage 2): Sequencing of ribosomal depleted RNA (Illumina Novaseq) with pathway analysis was performed, differentiation capacity was quantified histologically (Wilcoxon test), duplication rate was measured with CellTrace™ (t-test), and stem cell surface marker expression was quantified by flow cytometry (CD14, CD16, CD19, CD34, CD45, CD73, CD90, CD105, CD284 (t-test)).

Results: Biopsies: Collagen was qualitatively more abundant in MC1 than in Ctrl bone marrow, particularly in areas of adipocyte clusters and around adipocytes (Figure 1, arrows). FLIM was able to distinguish adipocytes (T =2.1-2.7ns), leukocytes (T =0.4-0.8ns), erythrocytes (T =0.2-0.4ns), and collagen (T <0.15ns) based on their different auto-fluorescent life-times (Figure 1, right).

BMSCs: By RNA sequencing 154 genes were differentially expressed between MC1 and Ctrl BMSCs ($p \leq 0.01$; $\log_2 \text{ratio} \geq 0.5$). Pathway analysis revealed significant alterations in processes important for 'cell adhesion' ($p < 9.3e-13$) and 'extracellular matrix organization' ($p < 1.8e-7$). Aggrecan (fold change=0.25, $p < 1e-7$) and osteopontin (fold change=5.26, $p < 1e-5$) were the first and third top-most differentially regulated genes, indicating a shift away from chondrogenic polarization towards osteogenic polarization. A shift in BMSC polarization was corroborated with differentiation assays: MC1 vs. Ctrl BMSCs had a reduced adipogenic (mean $\pm$ sd: -33 $\pm$ 13%, $p=0.03$) and chondrogenic (-31 $\pm$ 25%, $p=0.18$) differentiation capacity (Figure 2). In addition, an increased duplication rate of MC1 vs. Ctrl BMSCs (29.3 $\pm$ 1.7 vs. 26.2 $\pm$ 1.0 hours, $p=0.07$) was observed, also indicate a change in phenotype. There were no changes in the expression of surface markers.

Conclusion: These data suggest that MPE-FLIM is a prime technology to investigate fibrotic pathologies and it allows to morphologically study the importance of BMSCs in MC1. The BMSC/adipocyte axis seem to play a pivotal role in the fibrotic pathomechanism. Adipocytes have not been regarded as pathomechanistically relevant yet and hence open novel targets for therapeutic approaches.

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